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Short Original Communications

A Brain with Two Hypophyses in Median Cleft Face Syndrome*

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Summary. An unusual duplication of the hypophysis is described in a female baby aged 26 days with a median cleft face syndrome. Malformations of the cranium, brain, and spinal cord were confined to the ventral midline. These findings contrast to dysraphism, in which anomalies of dorsal neural and/or mesodermal structures are common. This rare condition of double hypophysis should also be classified among the midline cleft face syndrome in contrast to the formerly recorded cases of double hypophysis in partial twinning.

Key words: Double hypophysis – Dysraphism – Frontonasal dysplasia – Harmartoma of Hypothalamus – Heterotopia – Median cleft face syndrome

Duplication of parts of the central nervous system (CNS) has been observed occasionally. The classification of such malformations may have implications on pathogenetic mechanisms. A brain possessing two complete hypophyses, as described here, was found to have associated malformations of midline structures of the CNS and cranium.

Case Report

A female baby was the product of a 23-year-old mother who already had a healthy girl of 3 years. Hereditary diseases or malformations were not apparent in the family. The mother had surgery for an umbilical hernia in the early stage of her pregnancy. Pregnancy and delivery at term were without complications. The baby had Apgar's scores of 6/7/9 and, because of asphyxia, she received assisted respiration for several days until her discharge. She was re-admitted at the age of 26 days because of feeding difficulties. General examination revealed a V-shaped frontal hair line, hypertelorism, cleft palate with tumors inside the cleft, low-set ears, retrognathia, a wide prominent nasal root, a split on the top of the nose, and varus deformity of her right foot. Neurologic examination was normal. Laboratory data including chromosomal, amino acid, and blood analyses were all normal. The X-rays disclosed no clear contour of the sella and 11 ribs.

The baby was in no distress at the time of admission. Shortly after feeding, she was found dead in bed the same evening; efforts to resuscitate were without success.

Necropsy Findings

Body weight was 2,750 g and length 54 cm. The tongue was fixed by a persisting frenulum. The lungs showed mild acute edema without aspiration. Botallo's duct was open. Both ovaries were slightly hypertrophic but histologically normal.

Neuropathologic Findings

The head was not enlarged. The fontanelles were of normal size.

After removal of the brain, the sella appeared shallow and "empty". Instead, there were two sellae symmetrically situated on either side of the regular one, posterior to both optic canals. Both sellae contained a hypophysis each beneath the diaphragm (Fig. 1). Histologically, both hypophyses were completely normal (Fig. 3).

The distance between the optic canals was 2.3 cm (normal for that age: about 1.1 cm), that between the cribriform laminae was 2 cm (normal: about 0.8 cm). The abnormally short clivus had a midline defect, a hole, through which a stalk of connective tissue penetrated from the leptomeninx of the pontine base into the nasal cavity (Figs. 1, 4). Histologically, the connective tissue consisted of collagen fibers and striated muscle tissue with a small penetrating artery (Fig. 5). The posterior fossa was of normal size.

At the base of the brain (Fig. 2), the paired olfactory bulbs and nerves were set widely apart. The optic chiasma had a wide angle. There was a mass of hyperplastic gray matter which displaced the mamillary bodies laterally. The circle of Willis was abnormal: the basilar artery was very short (0.5 cm); the posterior communicating arteries were elongated. Between these communicating arteries and between both vertebral arteries, two masses of ectopic gray matter were located, measuring 2.5 mm × 4 mm and 3 × 5, respectively (Fig. 2). These contained nerve cells and myelinated nerve fibers (Fig. 8, 9).

The corpus callosum and posterior cingulate gyri were absent. On frontal sections, the ventricles appeared bat-winged (Fig. 6); Probst's bundles ran rostro-ventrally to the anterior wall of the third ventricle which was bounded by a thin membrane. The anterior commissure

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was also absent. The pineal body lay in its normal location. Between the laterally displaced mamillary bodies, a mass of hypothalamic tissue formed the base of the third ventricle (Fig. 6). This tissue contained magnocellular and medium-sized neurons without significant glial proliferation; irregular myelinated nerve fibers were also observed (Fig. 7). Posterior to the chiasma, two of hypophyseal stalks were verified histologically (Fig. 7).

The lamination of the cerebral cortex was normal for the age. Hypoxic changes were not apparent even in Ammon's horns. There were no developmental anomalies or secondary changes in either the white matter, basal ganglia, or thalamus.

At the levels of the midbrain and pons, there was a heterotopia in the tegmental raphe ventral to the aqueduct (Fig. 10). This heterotopia consisted of well myelinated nerve fibers, passing mostly axially, and of disseminated nerve cells.

The medulla oblongata showed a slit-like deep floor of the rhomboid fossa and both hypoglossal nuclei were separated by the deep medial sulcus (Fig. 11). Between the bottom of the median sulcus and the anterior median fissure there was heterotopic gray matter consisting of nerve cells of various size (Fig. 11).

The population of neurons in the inferior olivary nuclei was decreased and only cell islands were observed (Fig. 11). However, there was no astrocytic gliosis.

The cerebellum showed no abnormality except small matrix cell heterotopia in the dentate nuclei.

The spinal cord had a duplicated anterior median fissure at the cervico-thoracic level (Fig. 12). Between the two anterior median fissures there was hyperplastic grisea with myelinated fibers protruding from the central gray matter. In the upper cervical segments, hyperplastic gray matter protruded into the posterior tract where some heterotopic neurons were also found. Posterior roots entered the cord not only medially but also laterally to the posterior horn (Fig. 12).

Discussion

It should be noted that all malformations in the cranium and brain of our patient were found exclusively at the ventral median line of the calvarium and the CNS. Agenesis of corpus callosum has been observed as a single or associated anomaly in various cases and is not usually considered as a "ventral" midline malformation of the brain. However, the corpus callosum and anterior commissure arise, ontogenetically, ventrally from the region of the lamina terminalis (Hewitt 1962), so that this aplasia may also be theoretically considered as part of the ventral median cleft.

The duplication of the anterior median fissure of the spinal cord was insufficient to be regarded as "forme fruste" of a diastematomyelia (Hori et al. 1982). This malformation of the spinal cord also belonged to ventro-median anomalies.

Hyperplastic gray matter including that in the hypothalamus, in the tegmental raphe, and at the basal surface of the brain stem was also found in the midline. Polyposis inside the cleft palate might also be regarded as a feature of midline hyperplasia. Tegmental heterotopias observed in our patient were situated ventral to the aqueduct.

Because of all these features we felt that the complex of malformations found in our patient should be assigned to the median-cleft-face-syndrome group (DeMyer 1967), which includes median facial defects with hypertelorism, cranium bifidum occultum, V-shaped frontal hair line, median cleft nose, median cleft lip, and median cleft or absent premaxilla; some of these features may be absent as the term is used without regard to type and degree. The condition of ventral malformations in our patient contrasts the dysraphic states, in which malformations of neural as well as mesodermal tissues of the *dorsal* midline structures are characteristic.

The pathology in the inferior olivary nuclei differed from secondary nerve cell loss because reactive gliosis was absent. The preservation of islands of neurons after loss of nerve cells in this nucleus is unlikely; this finding also indicated an associating feature of dysgenesis. Matrix cell heterotopia in the dentate nucleus is a relatively common finding (Jellinger 1974; Friede 1973); hyperplasia of a posterior horn of the spinal cord

Fig. 1. Skull base with two hypophyses; in between is an empty sella. Note the wide distance between the cribriform laminae and optic canals. *Arrow*: midline defect of clivus

Fig. 2. The base of the brain shows a wide angle of the optic chiasma, duplicated pituitary stalks (*thick arrows*), hypothalamic hamartoma with lateral displacement of the mamillary bodies, long posterior communicating arteries (*broken lines*), and midline heterotopias on the base of brain stem (*small arrows*)

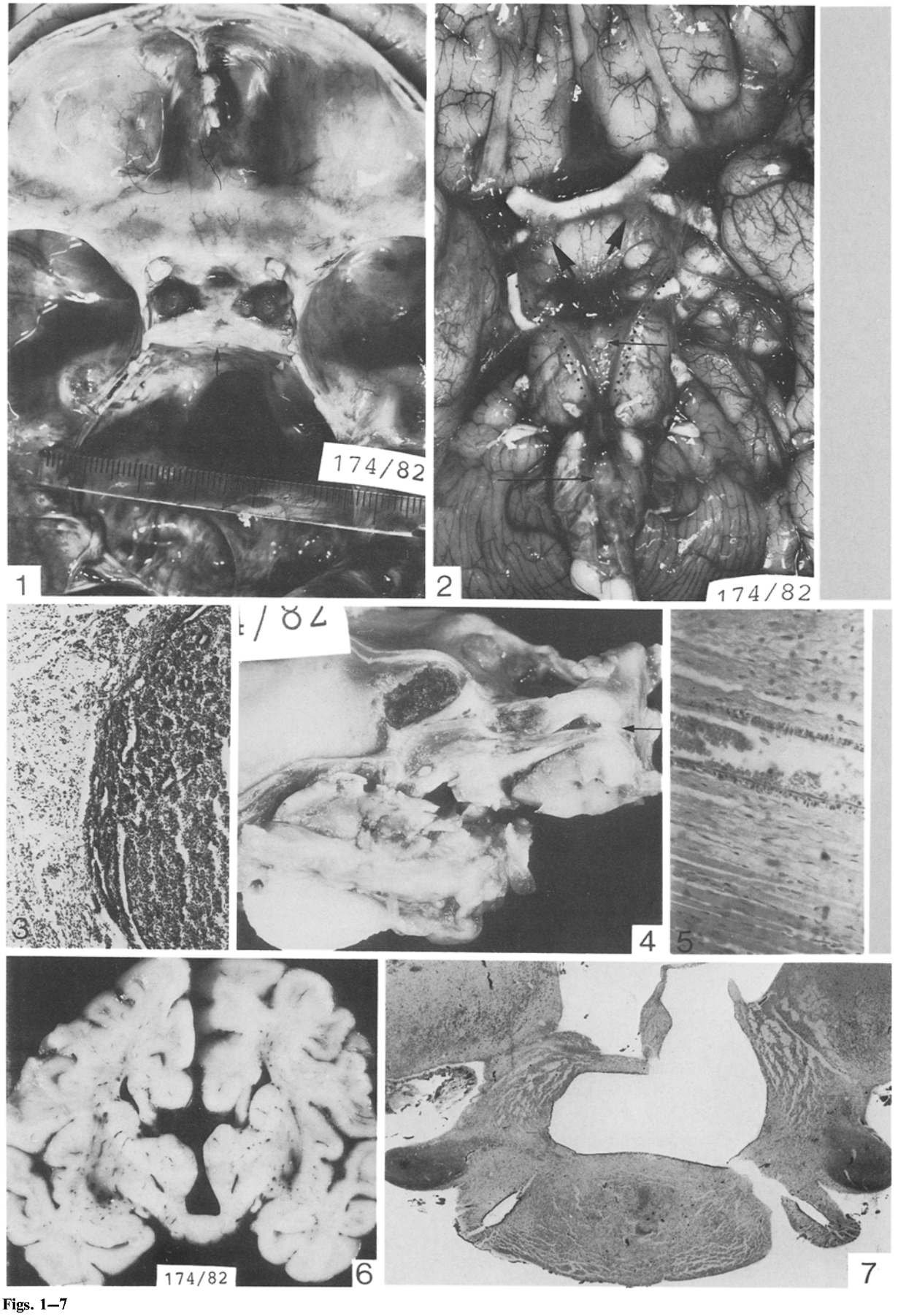
Fig. 3. Normal histology of left hypophysis (sagittal section). HE, × 57

Fig. 4. Sagittal section of skull base/clivus. Arrow indicates a hole through which connective tissue stretches from pontine basal leptomeninx to the nasal polyps, shown at the bottom of the picture

Fig. 5. Connective tissue strand in the hole (Fig. 4) contains heterotopic muscle tissue and probably a remnant ast of an embryonal artery. HE, × 142

Fig. 6. Frontal section reveals aplasia of the corpus callosum and a hypothalamic hamartoma displacing laterally the mamillary bodies

Fig. 7. Duplicated pituitary stalks. Inside the hypothalamic hamartoma, a few myelinated nerve fibers are visible. Klüver-Barrera, × 5.9



Figs. 1–7

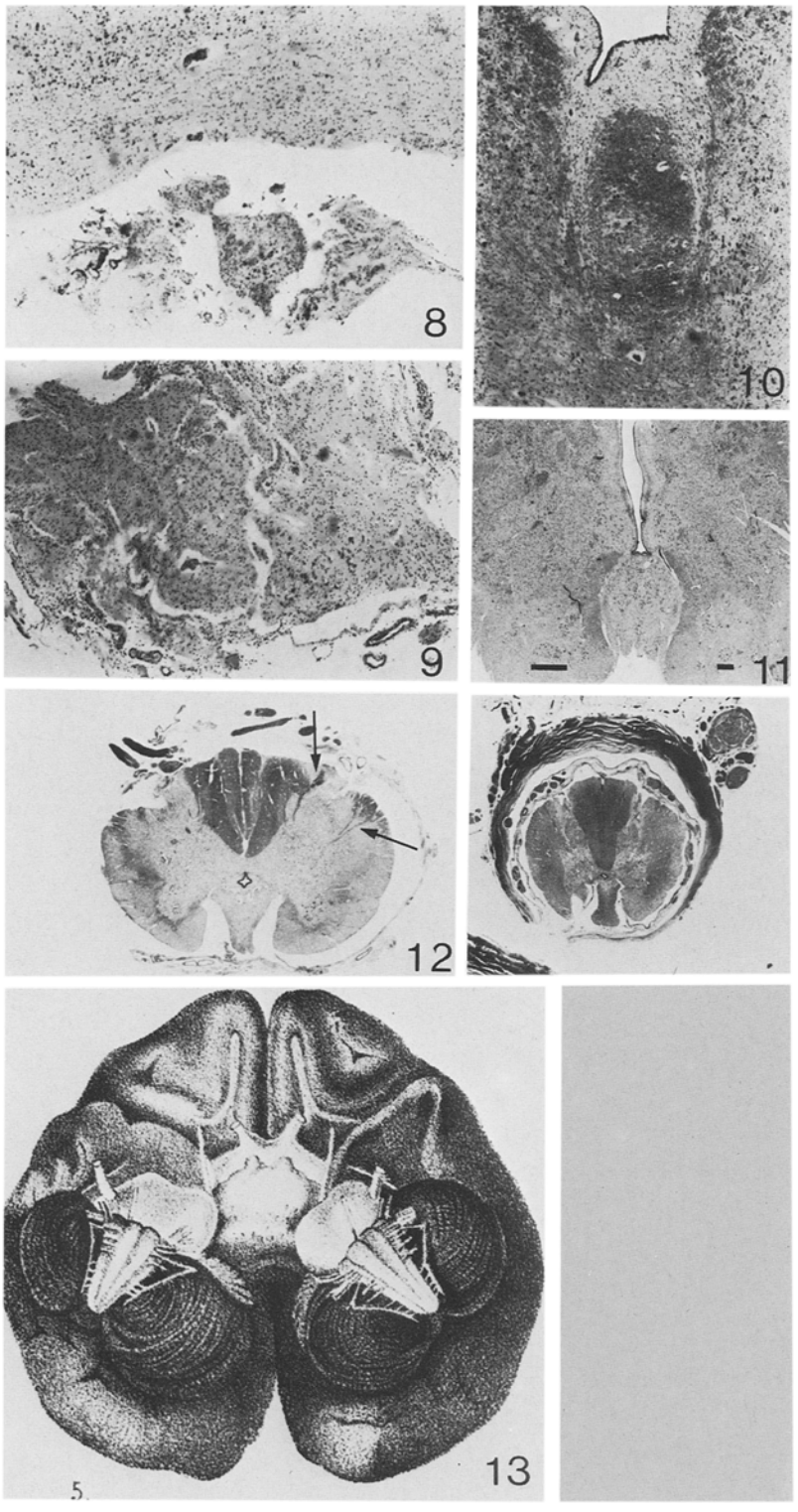


Fig. 8. Glio-neuronal heterotopia on the pontine base, shown in Fig. 2. Klüver-Barrera, ×23

Fig. 9. Identical heterotopia on the base of the medulla which contains nerve cells. HE, ×28

Fig. 10. Tegmental midline heterotopia at the level of the pons. Klüver-Barrera, ×23

Fig. 11. Deep rhomboid fossa with ventral midline heterotopia at the level of the hypoglossal nuclei. Island-like aggregations of nerve cells (marked by bars) are seen in the normal folded olivary nuclei. Klüver-Barrera, ×4.4

Fig. 12. Cervical and thoracic segments show a duplication of the anterior median fissure. *Arrows* indicate the posterior roots entering the cord dorsal and ventral to the posterior horn. Klüver-Barrera, ×5.3

Fig. 13. Probably the first record of double pituitary in a partial twinning by Ahlfeld in 1880

is also observed in 2% of normal human spinal cords (Hori 1981).

Duplication of hypophysis is extremely rare in humans, while it has been reported to occur in experimental animals (Tuchmann-Duplessis et al. 1974). The pathomorphogenesis of pituitary duplication in our patient might be discussed as follows: the pituitary anlage, both of neuro- and adeno-hypophysis, might have been divided during a stage of organogenesis due to the median cleft. Subsequent histogenesis of each

separate anlage might have caused duplication of the hypophysis. The histologically complete double hypophysis might possibly be correlated with the mass of the base of the hypothalamus. This hyperplasia of the hypothalamus might alternatively be interpreted as a ganglionic hamartoma without neoplastic proliferation or dedifferentiation of glio-neuronal elements. The first observation of human double hypophysis by Ahlfeld (1880) concerned a partial duplication of the brain (Fig. 13). Duplication of pituitary observed by Morton (1957) was also regarded as a part of partial twinning of minor degree. Warkany (1971) registered a similar condition in a case of a cephalopagus. These previous reports on double pituitary with partial twinning in various degrees contrasted our present case of median cleft face syndrome.

The median cleft face syndrome may physiognomically, and also neuropathologically, be considered opposite to the spectrum of holoprosencephaly, in which "cyclopia-hypotelorism" is characteristic (Friede 1975). Absence of the pituitary has been recorded in cyclopia (Edmonds 1950); this also contrasts the double pituitary in our patient with median cleft face syndrome. The term "frontonasal dysplasia" is used as a synonym for the median cleft face syndrome, though more in clinical aspects, and indicates malformations limited to the head (Sedano et al. 1970). "Median cleft face syndrome" encompasses, according to Gorlin et al. (1977), more than 100 various conditions, to which the case possessing two hypophyses reported here should belong as a unique variant.

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